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INTERMEDIATES FOR PREPARING PHENYLALKANOIC
ACIDS

(70)

Karady, Sandor, Elizabeth, New Jersey, U.S.A.,
Pines, Seemon H., Murray Hill, New Jersey, U.S.A.,
Ly, Manuel G., New Brunswick, New Jersey, U.S.A.,
and Sletzinger, Meyer, North Plainfield, New Jersey,
U.S.A.

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No. OF CLAIMS

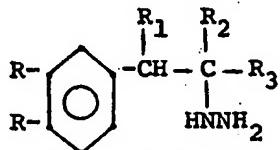
4 - No drawing

1 This invention describes a new method of prepar-
 2 ing certain α -hydrazino- β -phenylalkanoic acids and their
 3 derivatives. More particularly, it describes a method of
 4 preparing L- α -hydrazino- β -hydroxyphenylalkanoic acids and
 5 their derivatives. It further describes methods of prepar-
 6 ing certain chemical compounds which are new and useful
 7 intermediates in the synthesis of the above compounds.

8 It is known in the art that various α -hydrazino-
 9 β -phenylalkanoic acids are useful as decarboxylase inhibi-
 10 tors. It is further known that the D-isomer of these acids
 11 is generally inactive and may even be antagonistic to the
 12 action of the L-form, thereby reducing its potency.

13 This invention describes novel and useful chemical
 14 compounds and to the process for their preparation. More
 15 particularly, this invention describes novel compounds
 16 which are intermediates in the preparation of L- α -hydrazino-
 17 β -phenylalkanoic acids and their derivatives.

18 The present invention provides a new method of
 19 preparing the L-stereoisomeric compounds of formula I:



I

20 where

21 R is hydrogen or hydroxy;

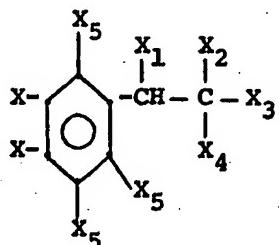
22 R₁ is hydrogen or lower alkyl;

23 R₂ is hydrogen or lower alkyl; and

- 1 R₃ is carboxy,
 2 loweralkoxycarbonyl,
 3 metalloxycarbonyl or
 4 amido.

5 It is to be understood that the L-configuration
 6 is in reference to the absolute configuration on the α-
 7 carbon in relation to the hydrazine.

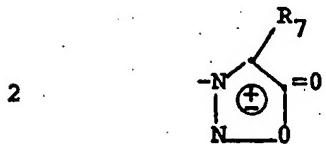
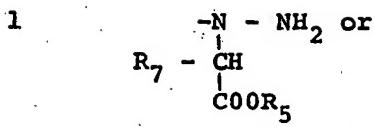
8 This invention further provides new methods of
 9 preparing valuable intermediate compounds which are useful
 10 in the preparation of the compounds of formula I. These
 11 intermediate compounds are the L-stereoisomeric compounds
 12 of formula II:



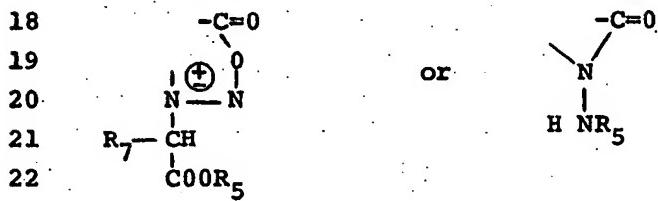
- 13 where
 14 X is hydrogen,
 15 hydroxy,
 16 lower alkoxy,
 17 aralkoxy or
 18 keto;
 19 X and X together are methylenedioxy;
 20 X₁ is hydrogen,
 21 lower alkyl,
 22 hydroxy,
 23 lower alkoxy or
 24 acyloxy;

- 1 X_2 is hydrogen,
 2 lower alkyl,
 3 hydroxyloweralkyl,
 4 haloloweralkyl,
 5 mercaptoloweralkyl,
 6 loweralkylthioloweralkyl,
 7 acyloxyloweralkyl or
 8 tosyloxyloweralkyl;
- 9 X_3 is carboxy,
 10 loweralkoxycarbonyl,
 11 aralkoxycarbonyl,
 12 metaloxycarbonyl,
 13 organocatoxycarbonyl,
 14 amido or
 15 cyano;
- 16 X_4 is $-\text{NHNHR}_5$,
 17 $-\text{NHNR}_6$,
 18 $\begin{matrix} -\text{NNH} \\ | \\ \text{R}_5 \end{matrix}$,
 19 $\begin{matrix} -\text{NNHR}_5 \\ | \\ \text{R}_5 \end{matrix}$,
 20 $-\text{NHNH}_2$,
 21 $-\text{N}=\text{NCH}_2\text{R}_7$,
 22 $\begin{matrix} -\text{N} & -\text{CH} & -\text{R}_7 \\ | & | & | \\ \text{NO}_2 & \text{R}_8 & \end{matrix}$,
 23 $\begin{matrix} -\text{N} & -\text{CHCOOH} \\ | & | \\ \text{NO} & \text{R}_7 \end{matrix}$,
 24 $\begin{matrix} \text{O} \\ | \\ -\text{N}=\text{NCH}_2\text{R}_7 \\ | \\ \text{O}^{\ominus} \end{matrix}$,
 25 $\begin{matrix} \text{O} \\ | \\ -\text{N}=\text{NCH}_2\text{R}_7 \\ | \\ \text{O}^{\ominus} \end{matrix}$,

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3 where R_5 is hydrogen, lower acyl or aralkyl,
 4 R_6 is aralkylidene (preferably o-phenylene-
 5 dimethylene and naphthylene and biphenyl
 6 homologs),
 7 R_7 is aryl and
 8 R_8 is halogen; and
 9 X_5 is hydrogen,
 10 halo,
 11 mercapto,
 12 loweralkylthio,
 13 aralkylthio or
 14 acylthio;
 15 X_1 and X_2 together are methylene, thus forming a cyclo-
 16 propyl ring; and
 17 X_3 and X_4 together are



23 where R_5 and R_7 are as described above.

24 We have found that the compounds of formula I can
 25 be conveniently prepared by reducing the intermediate

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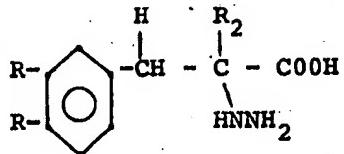
1 compounds of formula II. These valuable products are pre-
 2 pared without any appreciable disturbing of the rest of the
 3 molecule.

4 We have also found that the intermediate com-
 5 pounds of formula II can be conveniently prepared.

6 We have found that these intermediate compounds
 7 can be prepared in their desired L-stereoisomeric form.

8 We have further found that reduction of these L-
 9 stereoisomers can proceed smoothly to the desired L-stereo-
 10 isomer of the final product and thereby eliminate costly
 11 and complicated separation procedures.

12 A more preferred embodiment of this invention
 13 describes the preparation of the L-stereoisomeric compounds
 14 of formula III:



III

15 where R and R₂ are as described above.

16 A most preferred embodiment of this invention
 17 describes the preparation of L- α -(3,4-dihydroxybenzyl)- α -
 18 hydrazinopropionic acid and L- β -(3,4-dihydroxyphenyl)- α -
 19 hydrazinopropionic acid.

20 In the above descriptive portions of formulae
 21 I-III, the following definitions apply:

22 The "lower alkyl" radical signifies an alkyl
 23 group containing from 1 to about 6 carbon atoms which can

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1 be straight chained or branched.

2 The term "metal" refers to an alkali, alkaline
3 earth or aluminum metal.

4 The term "organocatoxy" refers to any organic
5 cation formed from a positively charged atom or radical such
6 as cyclohexylamine, triethylamine, phenethylamine and the
7 like. It is formed when these bases react with the
8 carboxyl group to form salts of the structure given in the
9 formula.

10 The "lower alkoxy" radical signifies an alkoxy
11 group containing from 1 to about 6 carbon atoms which can
12 be straight chained or branched.

13 "Aralkoxy" refers to an arylalkoxy group, the aryl
14 portion of which may be one or more phenyl or naphthyl
15 radicals attached to an α -alkoxy radical which contains
16 from 1 to about 4 carbon atoms. The preferable aralkoxy
17 groups are benzyl, diphenylmethyl, trityl, naphthylmethyl
18 and substituted benzyl and the like groups. Such sub-
19 stituents may include lower alkyl such as α -methylbenzyl,
20 lower alkoxy such as 3,4-veratryl and 4,4',4"-trimethoxy-
21 trityl and the like.

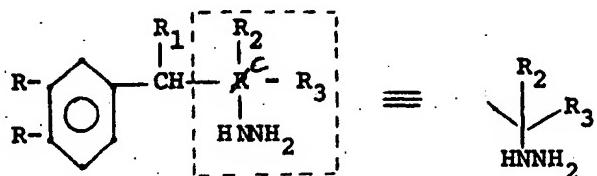
22 The "acyl" radical may be any organic radical de-
23 rived from an organic acid by the removal of the hydroxyl
24 group. It includes such radicals derived from carboxylic
25 acids, sulfonic acids and the like.

26 "Aryl" refers to phenyl, naphthyl and substituted
27 phenyl which may be lower alkyl or lower alkoxy sub-
28 stituents.

29 Each reductive method of preparation is described
30 by the specific reaction equation. For simplicity, when

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- 1 the preparation involves only the hydrazino-acid portion of
 2 the molecule, it is exemplified by only that part of the
 3 molecule in the reaction equation and it is to be under-
 4 stood that the remaining benzyl portion of the molecule
 5 remain intact:



- 6 where R, R₁, R₂ and R₃ are as described above, unless other-
 7 wise stated.

- 8 The following reactions describe the various
 9 methods of preparation of the compounds of this invention.

10 A. Removal of Protective Groups

11 a. Reduction to form the hydrazine moiety

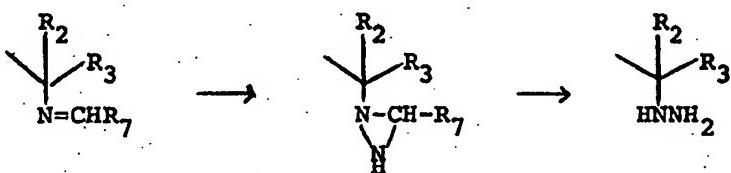
- 12 The reduction of various N-substituted hydrazino-
 13 acids and their derivatives results in the desired hydra-
 14 zino-acid or derivative. Reduction may be carried out
 15 using transition group methods as catalysts. Such sub-
 16 stituents which may be removed by catalytic reduction in-
 17 clude benzyl, trityl, diphenylmethyl, naphthylmethyl and
 18 substituted benzyl and the like groups. Such substitutes
 19 may include alkyl such as o-methylbenzyl, alkoxy such as
 20 3,4-veratryl, and 4,4',4"-trimethoxytrityl and the like.



- 21 where R₅ is aralkyl.

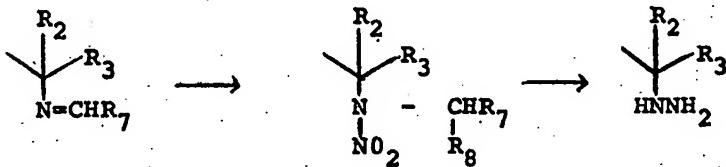
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1 A Schiff base can be prepared by condensing an α -
 2 aminoacid ester with benzaldehyde in the presence of di-
 3 cyclohexylcarbodiimide. Nitrene generated in situ can then
 4 add to this to prepare the hydrazino ester. When the ester
 5 group present is easily reduced (such as benzyl) the
 6 hydrazinoacid may be directly prepared.



7 A Schiff base may also be formed using diphenyl-
 8 ketone, diaralkylketone or an aralkylaldehyde in the pres-
 9 ence of an aminohalide or an aminoester halide.

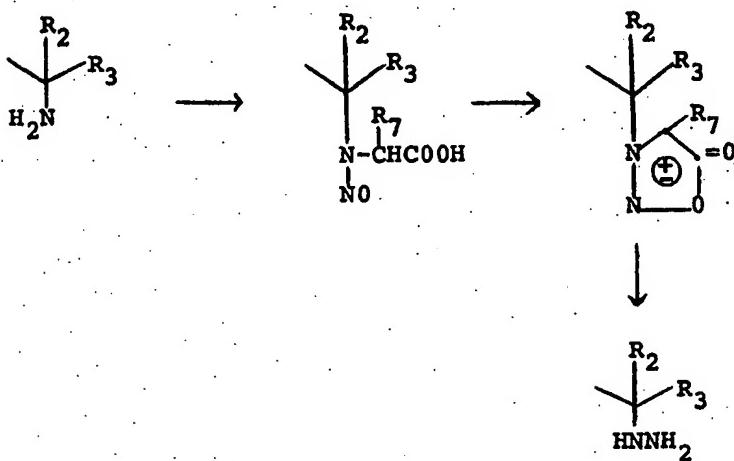
10 Alternatively, a pseudohalide such as iodoazide,
 11 iodothiocyanate, iodocyanate, iodonitrite and the like can
 12 be added to the Schiff base of above. Reduction by zinc in
 13 acetic acid followed by catalytic reduction with hydrogen
 14 and an active catalyst yields the hydrazinoester. When the
 15 ester group is easily reduced, the hydrazinoacid may be
 16 directly prepared.



17 Catalytic reduction with hydrogen over Raney
 18 nickel or an active catalyst on the sydnone-ester or syd-
 19 none-acid results in the desired hydrazinoester or hydra-
 20 zinoacid. When the ester group present is one that is
 21 easily reduced, the sydnone-ester may be directly reduced

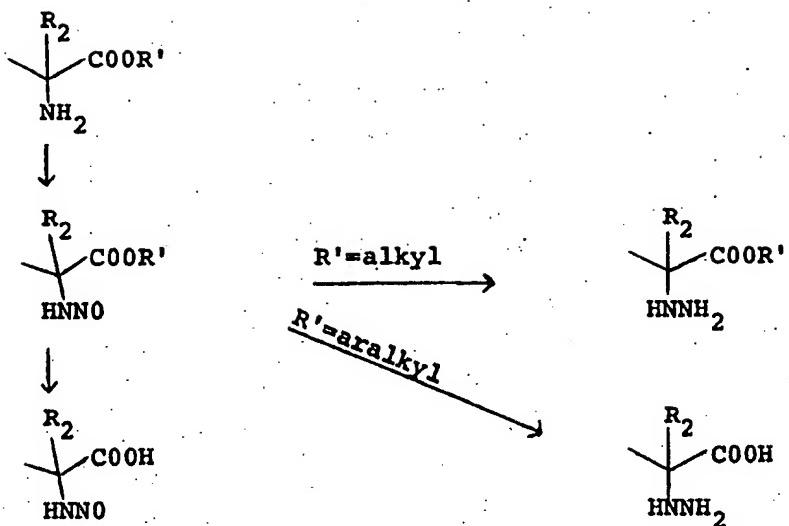
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- 1 to the hydrazinoacid. The sydnone may be prepared by con-
 2 densing an ester of the aminoacid with chlorophenylacetic
 3 acid in the presence of a hydrogen chloride acceptor. This
 4 intermediate may then be nitrosated and cyclized to the
 5 sydnone.



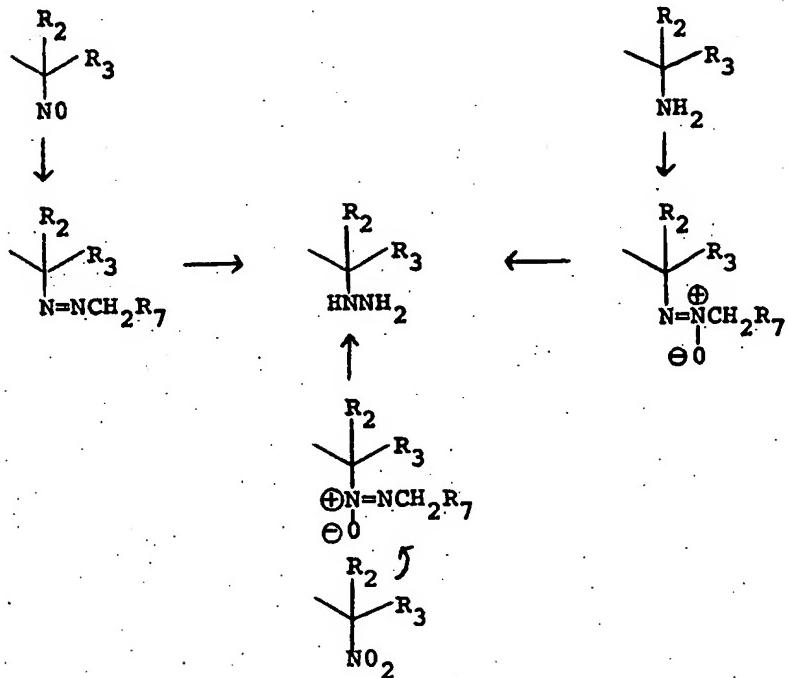
- 6 The α -alkyl aminoacid ester may be nitrosated in
 7 the usual way to the α -alkyl nitrosoamino-ester. Reduction
 8 using zinc catalyst results in the desired α -alkyl hydra-
 9 zinoester. When the ester group present is one that is
 10 easily hydrolyzed to the α -alkyl nitrosoamino-acid which
 11 may then be reduced to the α -alkyl hydrazinoacid as above.
 12 When the ester group present is one that is easily removed
 13 by reduction (such as benzyl) the α -alkyl nitrosoamino-
 14 ester may be directly reduced to the α -alkyl hydrazinoacid.

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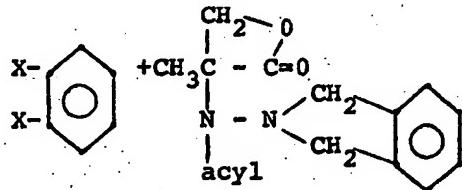
1 where R_2 is alkyl and R' is alkyl and aralkyl.

2 Other groups that may be catalytically reduced to
 3 the hydrazino compound are the aralkylazo and aralkylazoxy
 4 compounds. This reduction may be carried out with the acid
 5 or ester compounds. These compounds may be formed from
 6 the corresponding nitroso-, nitro- or aminoacid or -ester.

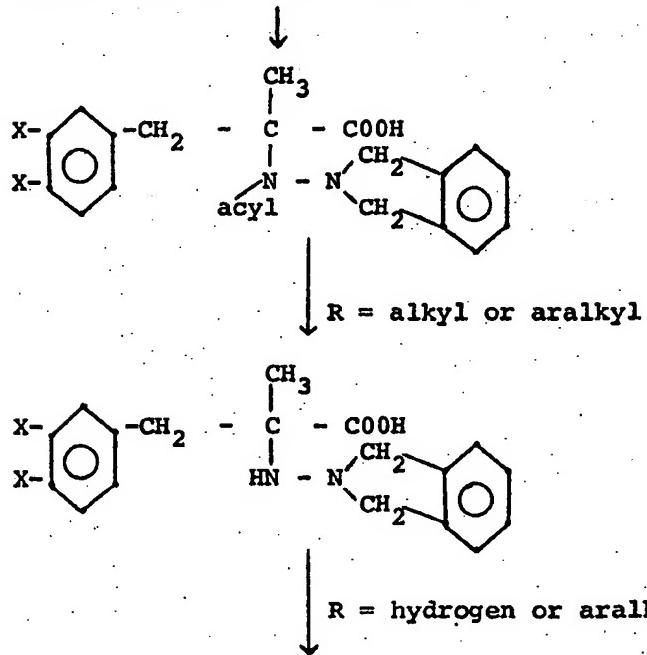


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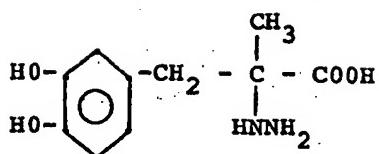
1 In a Friedel-Crafts reaction 1,2-dialkoxybenzene
 2 may be condensed with $\text{L-N}^1\text{-acyl-N}^2\text{-phenylenedimethylene-}$
 3 hydrazino- α -methylpropiolactone in the presence of alumini-
 4 um chloride. The alkoxy and acyl groups may then be re-
 5 moved with hydrobromic acid (preferably at raised tempera-
 6 ture). The phenylenedimethylene group is then removed by
 7 hydrogenation with a solid phase metal catalyst to obtain
 8 the desired hydrazine. If the alkoxy groups are replaced
 9 by aralkoxy groups, they may be removed simultaneously at
 10 the last step, if desired, to the hydroxy compounds. The
 11 above hydrogenation may also be carried out on the desired
 12 ester.



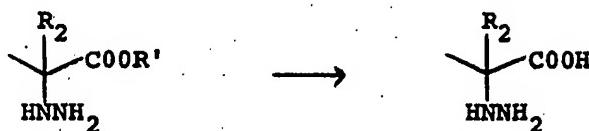
where X is alkoxy or aralkoxy



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1 b. Reduction to form the acid moiety

2 The reduction of various hydrazino-esters results
 3 in the hydrazino-acid compound. Reduction is preferably
 4 carried out using a solid phase metal catalyst. Such ester
 5 substituents which may be removed catalytically include
 6 benzyl, diphenylmethyl, trityl, naphthylmethyl and sub-
 7 stituted benzyl and the like groups. Such substituents may
 8 include alkyl such as α -methylbenzyl, alkoxy such as 3,4-
 9 veratryl and 4,4',4"-trimethoxytrityl and the like.



10 where R' is aralkyl.

11 c. Reduction to form the 3,4-dihydroxy moiety

12 Reduction to the 3,4-dihydroxy groups can be car-
 13 ried out on various 3,4-O-substituted compounds. This re-
 14 duction is preferably carried out using a solid phase metal
 15 catalyst on O-benzyl, O-diphenylmethyl, O-trityl, O-
 16 naphthylbenzyl and substituted O-benzyl and the like groups
 17 as above.

18 d. Reduction of two or more moieties

19 Simultaneous reduction may be carried out on more
 20 than one of the above moieties when one or more of the
 21 above groups are present in the compound. Thus, for example,

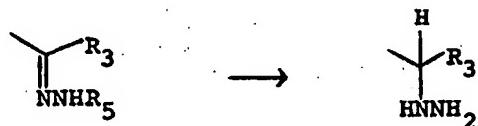
1 benzyl $\underline{\alpha}$ - $(3,4$ -dibenzylloxybenzyl)- α -N-benzylhydrazino-
 2 propionate may be catalytically reduced to $\underline{\alpha}$ - $(3,4$ -di-
 3 hydroxybenzyl)- α -hydrazinopropionic acid. Again, $\underline{\alpha}$ - 3 - $(\alpha$ -
 4 carbomethoxy- α -[$3'$, $4'$ -ditritylbenzyl])ethyl-4-phenyl-
 5 sydnone may be catalytically reduced as above to methyl $\underline{\alpha}$ -
 6 α - $(3,4$ -dihydroxybenzyl)- α -hydrazinopropionate.

7 B. Reduction of a double bond

8 When a double bond exists in the side chain, this
 9 may be hydrogenated over an optically active catalyst and
 10 crystallized to constant rotation to obtain the desired
 11 product. Thus, for example, α -N-benzylhydrazino- $3,4$ -di-
 12 benzylloxcinnamic acid can be hydrogenated in methanol over
 13 Raney nickel on lactose at 1-3 atmospheres and room tempera-
 14 ture to yield preponderantly $\underline{\alpha}$ - β - $(3,4$ -dihydroxyphenyl)- α -
 15 hydrazinopropionic acid.



16 Further, benzyl β - $(3,4$ -benzylloxyphenyl)- α -hydra-
 17 zonopropionate may also be treated in the same manner as
 18 above to give preponderantly $\underline{\alpha}$ - β - $(3,4$ -dihydroxyphenyl)- α -
 19 hydrazinopropionic acid.



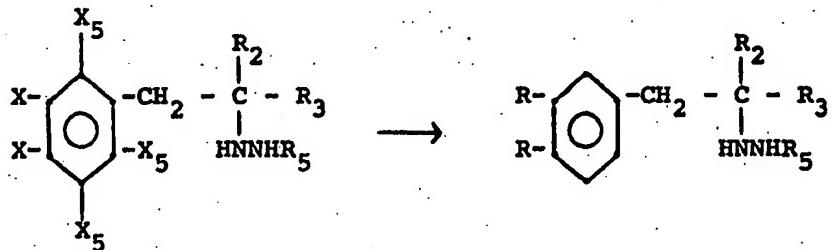
20 C. Removal of groups by reduction

21 a. From the phenyl moiety

22 The removal of various substituents on the benzene

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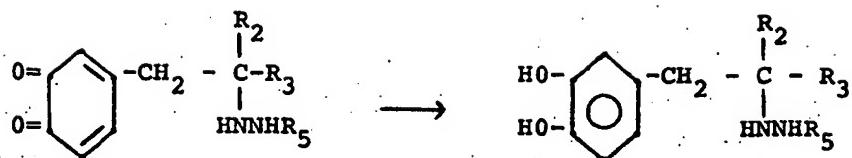
- 1 ring can be accomplished by reductive methods. Such groups
 2 as halogen, mercapto, alkylthio, aralkylthio, acylthio and
 3 the like may be removed by hydrogenation using an active
 4 catalyst.



- 5 When X is benzyloxy, R₅ is benzyl and R₃ is benzyloxycarb-
 6 only, the product obtained is β -(3,4-dihydroxyphenyl)- α -
 7 hydrazinopropionic acid.

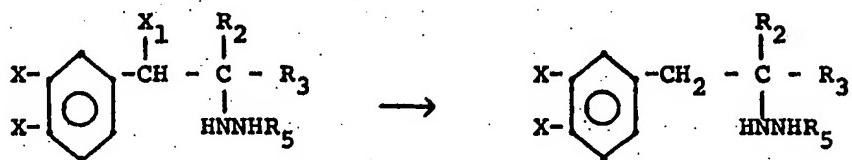
8 b. Reduction of a quinone

- 9 Reduction of quinone may be carried out on an α -
 10 benzoquinonyl moiety to obtain the α -dihydroxyphenyl moiety.
 11 The hydrazino group of the side chain must be protected
 12 since this is not capable of existing in the presence of
 13 the α -benzoquinonyl moiety. The reducing agent employed
 14 must be one having sufficient reducing potential to reduce
 15 the α -benzoquinonyl moiety without causing other changes in
 16 the molecule. The α -benzoquinone is in tautomeric equi-
 17 librium with the 3-hydroxyquinonemethide. The α -quinone
 18 may be reduced by chemical methods such as sulfur dioxide
 19 in water, zinc and dilute acetic acid, sodium hyrosulfite
 20 and other mild reducing agents. When the benzyl protective
 21 group is employed on the hydrazino group this may also be
 22 reduced off simultaneously.



1 c. From the side chain

2 Removal of various groups from the β -position of
 3 the side chain may be carried out reductively. Such groups
 4 as β -hydroxy, β -alkoxy or β -acyloxy may be removed using
 5 red phosphorous and hydriodic acid. The β -hydroxy group
 6 may also be converted to a β -chloro or β -bromo with phos-
 7 phorous trihalide and either in turn to β -iodo with potas-
 8 sium iodide in alcohol, whereupon reduction with red phos-
 9 phorous and hydriodic acid may proceed as before.



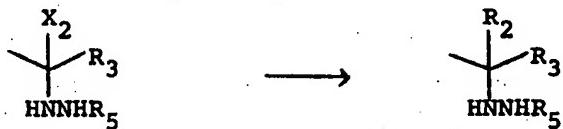
10 where X_1 is hydroxy, alkoxy or acyloxy. When X is benzyl-
 11 oxy, R_5 is benzyl and R_3 is benzyloxycarbonyl, the product
 12 obtained is β -(3,4-dihydroxyphenyl)- α -hydrazinopropionic
 13 acid.

14 d. Formulation of the α -alkyl group

15 Various α -substituted compounds can be reduced to
 16 the desired α -alkyl products of this invention. When the
 17 α -substituent is hydroxyalkyl this can be reduced to the α -
 18 alkyl product with red phosphorous and hydriodic acid. The
 19 chloroalkyl and bromoalkyl groups can be converted to iodo-
 20 alkyl by use of potassium iodide in alcohol. The mercapto-
 21 alkyl and alkylthioalkyl substituents may be desulfurized

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1 by the use of Raney nickel. Further, acetoxyalkyl or other
 2 acyloxy groups can first be hydrolyzed and alcohol treated
 3 as above or metathesized via the tosylate to the iodoalkyl
 4 which can then be treated with red phosphorous and
 5 hydriodic acid to the desired α -alkyl product. Depending
 6 on the desired end-product, the above reactions may be
 7 carried out on the ester and/or the substituted hydrazino
 8 compound. If the desired product is the α -alkyl acid and/
 9 or the free hydrazine, the starting material may have one
 10 or more groups present (such as benzyl) which can be re-
 11 moved simultaneously when the reduction of the α -substituent
 12 is carried out.



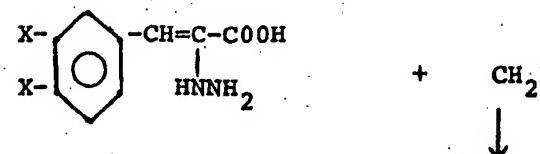
13 where X_2 is hydroxyalkyl, haloalkyl, mercaptoalkyl, alkyl-
 14 thioalkyl, acyloxyalkyl or tosyloxyalkyl; and R_2 is alkyl.

15 D. Ring cleavage of the side chain

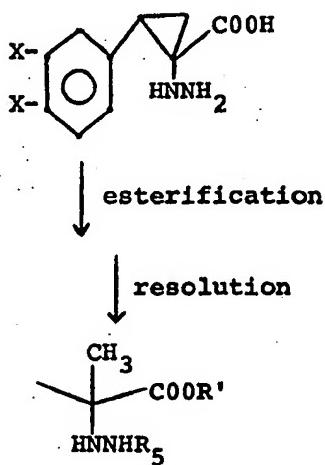
16 β -3,4-Diaralkoxyphenyl- α -hydrazinocyclopropane
 17 carboxylic acid can be prepared from cis-trans- α -hydrazino-
 18 3,4-diaralkoxycinnamic acid with methylene iodide and zinc.
 19 This cyclopropane acid, when converted to the methyl ester,
 20 can be resolved as the L-menthylloxyacetyl derivative. The
 21 methyl ester and menthylloxyacetyl groups can then be removed
 22 by acid hydrolysis. The aralkoxy groups and cyclopropane
 23 ring are then cleaved by hydrogenation over finely divided
 24 transition metals, preferably Raney nickel. When the benzyl
 25 ester is prepared in place of the methyl ester, the benzyl
 26 ester group may be removed by hydrogenation at the final
 27 step. When it is desired to obtain a final product which is

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- 1 the ester or substituted hydrazine, the desired substituents may be carried through the reaction sequence.

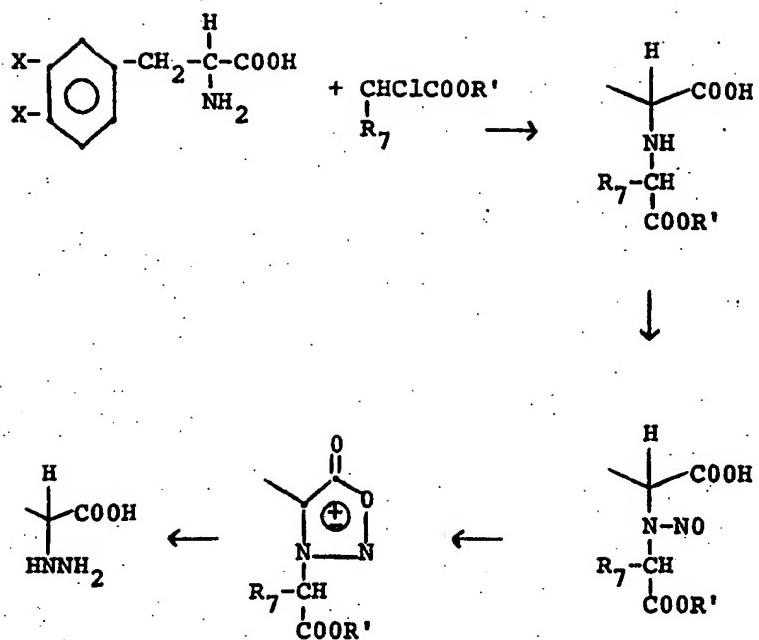


where X is aralkoxy

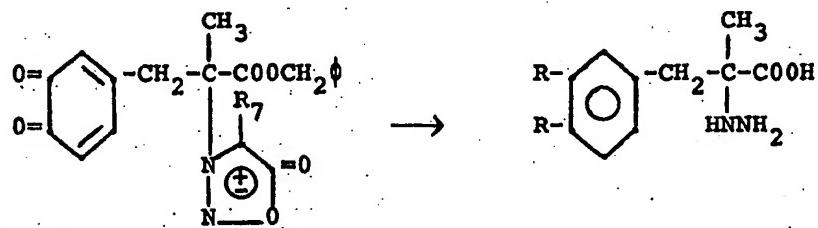


- 3 When DL-3,4-diaralkoxylphenylalanine is condensed
- 4 with an alkyl D- α -chlorophenylacetate in the presence of
- 5 pyridine as a hydrogen chloride acceptor, the N-(α -aryl-
- 6 acetate) derivative is obtained. It is preferable to use
- 7 the isopropyl ester. The L-adduct may then be nitrosated
- 8 and converted to the L-sydnone in the usual way with di-
- 9 cyclohexylcarbodiimide. Hydrogenation of the L-sydnone
- 10 with Raney nickel results in the L- β -(3,4-dihydroxyphenyl)-
- 11 α -hydrazinopropionic acid.

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- 1 where R' is alkyl.
- 2 Any combination sequence of the above reductive
- 3 reactions is also considered to be a part of this invention.
- 4 Thus, for example, L-3-[a-(3',4'-quinonylmethyl)-a-
- 5 benzyloxycarbonyl]ethyl-4-phenylsydnone may be hydrogenated
- 6 over Raney nickel to L-(3,4-dihydroxybenzyl)-a-hydrazino-
- 7 propionic acid.



- 8 It is preferred that the hydrogenation of this
- 9 invention be carried out at a sufficiently elevated tempera-
- 10 ture and over a sufficient time to form the desired end-
- 11 products and add hydrogen. The reaction is preferably

1 carried out at a temperature which is high enough so that
2 hydrogenation takes place readily. The reaction tempera-
3 tures can vary from below room temperature to about 300°C.,
4 although it is preferable to run the reaction at tempera-
5 tures from about -20°C. to 150°C.

6 It is also preferred that the invention take
7 place in an inert solvent. Any organic solvent which
8 would not cause adverse side-effects to take place can be
9 employed. It is most preferable to use a solvent which
10 would boil low enough to be easily removed from the
11 product. A solvent can be selected by first determining
12 the particular reaction temperature desired and then
13 choosing a solvent which will reflux at about that tempera-
14 ture and at 1 atmosphere. Typical solvents which can be
15 used are alcohols, dimethylsulfoxide, methylcellulose,
16 benzene, mono- and dialkylbenzene, dioxane, cyclohexane,
17 naphthalene, diglyme, triglyme, etc.

18 The amount of catalyst employed should be suffi-
19 cient to cause this hydrogenation to proceed. An excess
20 is preferably employed to insure a good yield of product.

21 The reaction is usually carried out at 1-3
22 atmospheres, however higher pressure may also be used.

23 Once the desired products are prepared, they can
24 be isolated from the reaction mixture by conventional
25 methods known in the art. One such method would involve
26 filtering the cooled reaction mixture, evaporating and
27 separating the product by extraction or chromatography.
28 The product formed can then be purified by recrystalliza-
29 tion from an appropriate solvent.

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1 The use of several heterogeneous catalysts that
2 may be employed include such catalysts as
3 (a) solid phase metal catalysts (such as platinum,
4 palladium, rhodium, ruthenium, etc.);
5 (b) active catalysts containing a metal catalyst on a
6 suitable carrier (such as 5-10% of a platinum metal on
7 carbon, 5-10% palladium-on-diatomaceous earth, or other
8 finely divided material);
9 (c) Raney nickel.

10 Other reductive methods employed will become
11 apparent to one skilled in the art.

12 The starting materials of this invention are
13 known or a reference to their preparation is included.

14 The following examples show the preparation of
15 the products of this invention. They are to be construed
16 as illustrative of the invention and not as limitations
17 thereof.

1

Example 1

2 To L-a-(3,4-dihydroxybenzyl)-a-ureidopropionic
3 acid [J. Med. Chem., 7, 379 (1964)] (25.4 g., 0.1 mole)
4 in 150 ml. of methanol is added 16.74 g. (0.31 mole) of
5 sodium methylate. With stirring 23.32 g. (0.2 mole) of
6 benzyl chloride is added dropwise and the mixture refluxed
7 for 4 hours. Water (200 ml.) is added and the mixture is
8 distilled until the boiling point reaches 95-98°C. By
9 addition of hydrochloric acid the pH of the mixture is
10 adjusted to 3.5, the volume adjusted to 200 ml. by addi-
11 tion of water and the mixture refluxed for 2 hours addi-
12 tional. After water is removed in vacuo, the mixture is
13 extracted with methanol and the methanol extract chromato-
14 graphed over silica gel. The eluate is concentrated to
15 obtain L-a-(3,4-dibenzylloxybenzyl)-a-ureidopropionic acid.

16 To an ice-cold mixture of the hydantoic acid of
17 the previous step (21.78 g., 0.05 mole) in 100 ml. of
18 2.5 N sodium hydroxide is added to a solution of sodium
19 hypochlorite (89.5 ml., 0.70 N, 0.0625 mole). After the
20 addition is completed, the mixture is stirred for 5 minutes
21 at 0 - 5°C. The mixture is then heated to 80°C. and main-
22 tained at 80°C. for 1.5 hours. At the end of this period,
23 300 ml. of toluene and 4 ml. of 85% hydrazine hydrate are
24 added and the mixture vigorously agitated while 54 ml. of
25 concentrated hydrochloric acid is added. The mixture is
26 stirred at 80°C. for 30 minutes, the phases separated and
27 the aqueous phase washed with 150 ml. of toluene. The
28 aqueous phase is evaporated to dryness, the residue ex-
29 tracted with methanol and the pH of the extract adjusted
30 to 6.4 with diethylamine. The product is separated by

1 filtration and recrystallized from methanol-water to
 2 obtain L- α -(3,4-dibenzylloxybenzyl)- α -hydrazinopropionic
 3 acid. A solution of L- α -(3,4-dibenzylloxybenzyl)- α -hydra-
 4 zinopropionic acid (8.13 g., 0.02 mole) in 200 ml. of
 5 acetic acid is hydrogenated over 0.5 g. of 5% palladium
 6 on charcoal at room temperature and 3 atm pressure. The
 7 catalyst is removed by filtration, washed and the filtrate
 8 concentrated to yield L- α -(3,4-dihydroxybenzyl)- α -hydra-
 9 zinopropionic acid, m.p. 208°C. dec.

10

11 When benzyl chloride in the above example is
 12 replaced by diphenylmethylchloride, trityl bromide, α -naph-
 13 thylmethyl bromide, o-tolyl chloride, 3,4-veratyl bromide
 14 or 4,4',4"-trimethoxytrityl bromide, the corresponding
 15 L- α -(3,4-disubstitutedbenzyl)- α -hydrazinopropionic acid is
 16 prepared which is then reduced to L- α -(3,4-dihydroxybenzyl)-
 17 α -hydrazinopropionic acid.

18

Example 2

19 L- α -amino- α -(3,4-dibenzylloxybenzyl)-propionic
 20 acid hydrochloride salt (44.1 g., 0.1 mole) is slurried
 21 in benzene (300 ml.) and 10.1 g. (0.1 mole) of triethylamine
 22 is added dropwise with cooling to 10-15°C. After
 23 addition of 10.6 g. of benzaldehyde, 20.6 g. (0.1 mole)
 24 of dicyclohexylcarbodilimide in 25 ml. of benzene is added
 25 and the mixture stirred 18 hours at room temperature with
 26 the exclusion of moisture. The mixture is filtered, washed
 27 and the filtrate concentrated in vacuo.

28 To the resulting Schiff base in 100 ml. of ether
 29 containing 0.1 mole of ammonia is added 0.1 mole of chlor-
 30 amine ca. 0.35 N in ether. After a short time ammonium

1 chloride begins to separate. The mixture is allowed to
 2 stand overnight, filtered and the precipitate washed with
 3 ether. The ethereal solution is partially concentrated in
 4 vacuo, extracted with water, the ethereal extract dried
 5 (K_2CO_3), filtered and concentrated in vacuo. A solution
 6 of L- α -(3,4-dibenzylloxybenzyl)- α -3-(phenyldiaridinyl)-
 7 propionic acid (9.89 g., 0.02 mole) in acetic acid (200 ml.)
 8 is hydrogenated over 0.7 g. of 5% palladium on charcoal at
 9 room temperature (25°C.) and 3 atm. pressure. The catalyst
 10 is removed by filtration, washed and the filtrate taken to
 11 dryness in vacuo. The residue is crystallized from water to
 12 obtain L- α -(3,4-dihydroxybenzyl)- α -hydrazinopropionic acid,
 13 m.p. 208°C. dec.

14 When dibenzylketone, diphenylketone or α -phenyl
 15 acetaldehyde are used in place of benzaldehyde in the above
 16 procedure, the corresponding Schiff base is prepared which
 17 is then reduced to L- α -(3,4-dihydroxybenzyl)- α -hydrazino-
 18 propionic acid.

19 When methyl L- α -amino- α -(3,4-dibenzylloxybenzyl)-
 20 propionate or L- α -amino- β -(3,4-dibenzylloxyphenyl)propionic
 21 acid are used in place of L- α -amino- α -(3,4-dibenzylloxy-
 22 benzyl)propionic acid, the product obtained is methyl L- α -
 23 (3,4-dihydroxybenzyl)- α -hydrazinopropionate or L- β -(3,4-
 24 dihydroxyphenyl)- α -hydrazinopropionic acid.

25 Example 3

26 To L- α -benzylideneamino- α -(3,4-dimethoxybenzyl)-
 27 propionic acid, methyl ester (34.14 g., 0.1 mole) in ether

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1 (500 ml.) and under nitrogen, is added silver nitrate
2 (22.1 g., 0.13 mole) and iodine (33.0 g., 0.13 mole). The
3 mixture is stirred at room temperature (25°C.) for 18 hours,
4 filtered, the precipitate washed with ether and the ethereal
5 filtrate washed with ice-cold dilute sodium bisulfite.
6 The ethereal solution is dried (sodium sulfate) and con-
7 centrated to dryness in vacuo to obtain L- α -(3,4-dimethoxy-
8 benzyl)- α -N- α' -iodobenzyl-N-nitroalanine methyl ester. A
9 mixture of zinc dust (26.2 g., 0.4 mole) and water (100 ml.)
10 is cooled to 10°C. and to it is added with stirring and
11 while maintaining the temperature at 10-15°C., the ester
12 from the previous step (51.4 g., 0.1 mole) dissolved in
13 acetic acid (200 ml.) is added. After addition is ended,
14 the mixture is slowly warmed to 25°C. over an hour and then
15 to 80°C. on the steam-bath. The mixture is cooled to
16 35°C., filtered to remove unreacted zinc. The precipitate
17 is washed with three 25 ml. portions of warm 2 N hydro-
18 chloric acid and the combined filtrate is heated at reflux
19 for 3 hours. The mixture is cooled to 20°C., basified with
20 sodium hydroxide to pH 6.5, filtered, washed and the pre-
21 cipitate dried in air. The solid is extracted with three
22 200 ml. portions of chloroform, dried (magnesium sulfate)
23 and the extract concentrated to dryness in vacuo. The
24 residue is recrystallized from methanol-water to obtain L-
25 α -(3,4-dimethoxybenzyl)- α -N¹-benzylhydrazinopropionic acid.

26 The acid from the previous step (10.75 g., 0.03
27 mole) is refluxed for 2 hours with constant boiling hydro-
28 bromic acid (50 ml.). The mixture is concentrated to dry-
29 ness in vacuo, flushed with t-butanol and dried to yield
30 crude L- α -(3,4-dihydroxybenzyl)- α -N¹-benzylhydrazino-

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1 propionic acid hydrobromide salt.

2 The salt from the previous step is dissolved in
3 200 ml. of acetic acid and hydrogenated over 1.0 g. of 5%
4 palladium-on-charcoal at room temperature and 3 atmospheres
5 pressure. The mixture is vented, filtered, the precipi-
6 tate washed and the combined filtrates taken to dryness in
7 vacuo. The residue is dissolved in methanol and the mix-
8 ture brought to pH 6.5 by addition of diethylamine. L-
9 (α -(3,4-dihydroxybenzyl)- α -hydrazinopropionic acid is sepa-
10 rated by filtration and recrystallized from water contain-
11 ing 0.5% sodium bisulfite, m.p. 208°C. dec.

12 When L- α -benzylideneamino- β -(3,4-dimethoxyphenyl)-
13 propionic acid methyl ester is used in the above example,
14 the product prepared is L- β -(3,4-dihydroxyphenyl)- α -hydra-
15 zinopropionic acid.

16 Example 4

17 To a solution of L- α -amino- α -(3,4-dibenzoyloxy-
18 benzyl)propionic acid [J. Org. Chem., 29, 1424 (1964)]
19 (39.1 g., 0.10 mole) in 50 ml. of methyl alcohol is added
20 gaseous hydrogen chloride until the saturation point is
21 reached. The mixture is stirred at room temperature for
22 24 hours, then concentrated to dryness.

23 To the residue dissolved in 100 ml. of methanol
24 is added with cooling 20.2 g. (0.2 mole) of triethylamine
25 and 17.06 g. (0.1 mole) of α -chlorophenylacetic acid. The
26 mixture is heated at reflux for 5 hours, cooled to 10°
27 and acidified to pH 3.5 with 6 N hydrochloric acid. The
28 mixture is concentrated in vacuo to remove methanol, the

1 residue diluted with water and extracted with chloroform.
2 After drying over magnesium sulfate, the chloroform is
3 removed in vacuo and the residue crystallized from acetone-
4 hexane.

5 To a slurry of 30 g. (0.05 mole) of intermediate
6 from the previous step in 150 ml. of water is added 4.25
7 ml. of concentrated hydrochloric acid and 500 ml. of ether.
8 The mixture is cooled to 0°C. and 3.8 g. (0.055 mole) of
9 sodium nitrite in 10 ml. of water is added dropwise over
10 30 minutes. Stirring at 0°C. is continued for 3 hours. The
11 ether layer is separated and the aqueous layer is extracted
12 with ether. The combined ethereal extract is extracted
13 with saturated salt solution and the ethereal solution
14 dried over magnesium sulfate and concentrated in vacuo.
15 The residue is dissolved in 500 ml. of benzene and 10.3 g.
16 (0.05 mole) of dicyclohexylcarbodiimide in 140 ml. of
17 benzene added. The mixture is heated with stirring at 50-
18 60°C. for 2 hours, filtered hot and washed with benzene. The
19 filtrate is cooled to room temperature, washed with water,
20 dried and concentrated in vacuo. The residue is recrys-
21 tallized from acetone-hexane to yield L-3-[α -benzyloxy-
22 carbonyl- α -(3',4'-dibenzyloxybenzyl)]ethyl-4-phenylsydnone.

23 To a solution of 31.9 g. (0.05 mole) of the fore-
24 going sydnone in 250 ml. of benzene and 50 ml. of glacial
25 acetic acid is added 1.5 g. of Raney nickel. The mixture
26 is hydrogenated at room temperature until the uptake is
27 0.3 mole. The mixture is warmed to 60°C., filtered and
28 washed. The combined filtrate is diluted with water and
29 brought to pH 7 by addition of 40% sodium hydroxide with
30 stirring and cooling. The layers are separated, the aqueous

1 extracted with benzene, the combined benzene extracts dried
2 over magnesium sulfate and concentrated to dryness in
3 vacuo to obtain L- α -(3,4-dihydroxybenzyl)- α -hydrazino-
4 propionic acid (m.p. 208°C. dec.).

5 When L- α -amino- β -(3,4-benzyloxyphenyl)propionic
6 acid or L- α -amino- β -(3,4-dimethoxyphenyl)propionic acid
7 is used in place of L- α -amino- α -(3,4-dibenzylloxybenzyl)-
8 propionic acid in the above example, the product obtained
9 is L- β -(3,4-dihydroxyphenyl)- α -hydrazinopropionic acid.

10 Example 5

11 To a mixture of 23.9 g. (0.1 mole) of L- α -methyl-
12 3,4-dibenzylloxyphenylalanine [J. Org. Chem., 29, 1424
13 (1964)] in 200 ml. of 75% acetic acid at 0-10°C. is added
14 10.35 g. (0.15 mole) of sodium nitrite in 20 ml. of water.
15 When the addition is complete, the mixture is stirred for 4
16 hours at 5 to 10°C. Zinc dust (52.4 g., 0.8 mole) is added
17 with stirring while maintaining the temperature between 10
18 and 15°C. After the addition is finished, the mixture is
19 allowed to warm to room temperature over an hour and then
20 warmed to 80°C. on the steam-bath. The mixture is filtered
21 to remove unreacted zinc and the precipitate washed with
22 three 25 ml. portions of warm 2 N hydrochloric acid. The
23 combined filtrate is cooled to room temperature and with
24 cooling basified to pH 6.5. The mixture is filtered and the
25 precipitate dried. The residue is extracted with three 200
26 ml. portions of chloroform. The dried magnesium sulfate
27 extract is concentrated in vacuo to a residue which is
28 recrystallized from methanol to yield L- α -(3,4-dibenzylloxy-
29 benzyl)- α -hydrazinopropionic acid. This material is hydro-
30 genated as in Example 2 to yield L- α -(3,4-dihydroxybenzyl)-

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1 α -hydrazinopropionic acid (m.p. 208°C.).

2 When the methyl ester of L- α -methyl-3,4-dibenzyl-
3 oxyphenylalanine is used in place of the acid in the above
4 procedure, the product obtained is methyl L- α -(3,4-di-
5 hydroxybenzyl)- α -hydrazinopropionate.

6 Example 6A

7 L- α -Methyl-3,4-dihydroxyphenylalanine sesqui-
8 hydrate [J. Org. Chem. 29, 2503 (1964)] (119.1 g., 0.5
9 mole), phenylnitrosomethane dimer (60.57 g., 0.25 mole)
10 and 500 ml. of toluene are placed in a flask and refluxed.
11 By means of a Dean-Stark separator, water is azeotroped
12 away and toluene is returned to the flask. When the
13 theoretical amount of water (1.25 moles) is distilled, L-
14 α -(benzylazo)- α -(3,4-dihydroxybenzyl)propionic acid is
15 obtained on concentration of the mixture to dryness in
16 vacuo at a temperature <50°C.

17 The acid (31.4 g., 0.1 mole) in 300 ml. methanol
18 containing 3 g. polyvinyl alcohol-20, 1 g. platinum oxide
19 and 3 g. vanadium (II) chloride is hydrogenated at 1 atm.
20 pressure and 80°C. until the uptake of hydrogen is 0.3 mole.
21 The mixture is cooled to room temperature, filtered, the
22 precipitate washed and the filtrate taken to dryness in
23 vacuo. The residue is recrystallized once from water and
24 a second time from water containing 0.5% sodium bisulfite
25 to yield L- α -(3,4-dihydroxybenzyl)- α -hydrazinopropionic
26 acid, m.p. 208°C. dec.

27 Example 6B28 L- α -Methyl-3,4-dihydroxyphenylalanine sesqui-

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1 hydrate (119.1 g., 0.5 mole), phenylnitromethane (68.57 g.,
2 0.5 mole) and 500 ml. of toluene are placed in a flask and
3 refluxed. The condensate is passed through a Dean-Stark
4 separator such that water is removed and toluene is returned
5 to the flask. L- α -(3,4-dihydroxybenzyl)- α -phenylazoxy-
6 propionic acid need not be isolated. To the mixture is
7 added 1.5 g. of platinum oxide and the mixture is
8 hydrogenated at 1 atm. of hydrogen and room temperature
9 until the uptake is 1.5 moles of hydrogen (in addition to
10 that needed to reduce the platinum oxide). The mixture is
11 concentrated to dryness in vacuo and the residue extracted
12 with hot methanol and filtered. The methanolic filtrate
13 is concentrated to dryness in vacuo and the residue crys-
14 tallized from water containing alkali-metal bisulfite to
15 yield L- α -(3,4-dihydroxybenzyl)- α -hydrazinopropionic acid,
16 m.p. 208°C. dec.

17 When L- β -(3,4-dihydroxyphenyl)alanine is used in
18 place of L- α -methyl-3,4-dihydroxyphenylalanine in the above
19 procedures, the product prepared is L- β -(3,4-dihydroxy-
20 phenyl)- α -hydrazinopropionic acid.

21 Example 7

22 To L-O,N-diacetyl- α -methylserine [Chem. Pharm.
23 Bull. (Japan), 15, 1776 (1967)] (101.6 g., 0.5 mole) in
24 500 ml. of pyridine is added N-chloroisindoline (77 g.,
25 0.5 mole) and the mixture is refluxed for 5 hours. The
26 mixture is concentrated to dryness in vacuo, taken up in
27 chloroform-water and washed with dilute hydrochloric acid,
28 water and saturated salt solution. The chloroform phase

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1 is dried over sodium sulfate, concentrated to dryness in
2 vacuo and the residue recrystallized from methanol-water to
3 yield L-a-N¹-acetyl-N²-phenylenedimethylenehydrazino-a-
4 methyl-0-acetoxypropionic acid.

5 The acid from the previous step (139.3 g., 0.4
6 mole) is refluxed with 100 ml. of acetic acid and 900 ml.
7 of 1 N hydrochloric acid for 3 hours. The mixture is
8 cooled to room temperature, washed and dried at 50°C. in
9 vacuo to yield L-a-N¹-acetyl-N²-phenylenedimethylene-
10 hydrazino-a-methylhydracrylic acid.

11 The acid from the previous step (92.0 g., 0.3
12 mole) and dicyclohexylcarbodiimide (66.0 g., 0.32 mole) in
13 500 ml. of benzene are stirred at room temperature for 24
14 hours. The mixture is filtered, water added to the
15 filtrate and the benzene phase successively washed with 5%
16 sodium bicarbonate, water and saturated salt solution.
17 The benzene phase is dried over magnesium sulfate and con-
18 centrated in vacuo and the residue recrystallized from
19 ethyl acetate-n-hexane to yield L-a-N¹-acetyl-N²-phenylene-
20 dimethylenehydrazino-a-methylpropiolactone.

21 To the lactone from the previous step (57.65 g.,
22 0.2 mole) and veratrole (182.3 g., 1.32 moles) is added all
23 at once 100 g. (0.75 mole) of aluminum chloride. The mix-
24 ture is heated at 80°C. for 4 hours, poured over ice and
25 extracted with ether. The ethereal solution is extracted
26 3 times with cold 1 N sodium hydroxide. The aqueous phase
27 is acidified with concentrated hydrochloric acid and
28 extracted with ether, the ether extract washed with water,
29 dried over sodium sulfate and concentrated in vacuo. The
30 residue is crystallized from methanol-water to yield L-a-

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1 (N¹-acetyl-N²-phenylenedimethylenehydrazino)-α-(3,4-di-
2 methoxybenzyl) propionic acid.
3 A mixture of L-α-(N¹-acetyl-N²-phenylenedimethyl-
4 enehydrazino)-α-(3,4-dimethoxybenzyl) propionic acid
5 (37.8 g., 0.1 mole) and 500 ml. of concentrated hydrochloric
6 acid is heated in a sealed tube at 120°C. for two hours. The
7 resulting mixture is evaporated to dryness in vacuo and
8 the product leached out with ethanol. The hydrazino acid
9 is precipitated by addition of diethylamine to pH 6.4,
10 the mixture filtered and the precipitate washed with
11 ethanol and dried to yield L-α-(N²-phenylenedimethylene-
12 hydrazino)-α-(3,4-dihydroxybenzyl) propionic acid.

13 The residue from above (32.84 g., 0.1 mole) is
14 dissolved in 400 ml. of methanol and hydrogenated over 5%
15 palladium-on-barium sulfate at 3 atmospheres and 80°C.
16 The mixture is cooled, filtered, the precipitate washed
17 with methanol and the filtrate concentrated in vacuo. The
18 residue is recrystallized from water containing 0.5%
19 sodium bisulfite to yield L-α-(3,4-dihydroxybenzyl)-α-
20 hydrazinopropionic acid (m.p. 208°C. dec.).

21 When L-0,N-diacetylserine is used in place of L-
22 0,N-diacetyl-α-methylserine in the above example, the
23 product obtained is L-β-(3,4-dihydroxyphenyl)-α-hydrazino-
24 propionic acid.

25 Example 8

26 Hydrazinium cis-trans 3,4-dibenzoyloxy-α-hydrazino-
27 cinnamate (42.25 g., 0.1 mole) in methanol (200 ml.) is
28 hydrogenated at room temperature (25°C.) and 3 atmospheres
29 over 1.0 g. of 25% palladium-on-silk [prepared according to

1 Akibori et al., Nature 178, 323 (1956)] until the uptake
2 is 0.3 mole of hydrogen. The mixture is filtered, washed
3 and concentrated to dryness in vacuo. The residue is taken
4 up in methanol and brought to pH 6.4 with methanolic
5 hydrogen chloride. The precipitate is separated by filtra-
6 tion and dried in air, resulting in preponderantly L-a-
7 (3,4-dihydroxyphenyl)-a-hydrazinopropionic acid. The
8 product is obtained after four recrystallizations from
9 water containing 0.5% sodium bisulfite.

10

Example 9

11 To a solution of 114.52 g. (0.50 mole) of 6-
12 bromopiperonal [J. Chem. Soc., 111 946 (1917)] is added
13 67.5 g. (0.90 mole) of nitroethane, 4.1 ml. n-butylamine
14 and 4.85 ml. of glacial acetic acid. The mixture is
15 refluxed and water is removed azeotropically. After the
16 theoretical amount of water has been distilled, distillation
17 is continued and finished at room temperature in vacuo.
18 Upon trituration of the residue with hexane, the β -methyl-
19 β -nitrostyrene is obtained in a crystalline state. In gen-
20 eral, however, the residue dissolved in toluene (90 ml.)
21 is sufficiently pure for the next step.

22 To a mixture of 246 g. of 40-mesh iron, 5 g. of
23 hydrated ferric chloride and 310 ml. of water, there is
24 added 125 g. of nitroolefin in 90 ml. of toluene. The mix-
25 ture is heated to reflux and 446 ml. of concentrated
26 hydrochloric acid is added dropwise at such a rate as to
27 maintain vigorous reflux. After the addition of acid is
28 ended refluxing is continued for three hours. A silicaceous
29 filter aid is added and the mixture is filtered. The
30 residue is washed with four 160 ml. portions of benzene.

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1 The combined benzene extracts are extracted with four 180
2 ml. portions of water. The benzene layer is stirred 1 hour
3 with 415 ml. of 10% sodium bisulfite solution. The benzene
4 phase is separated and washed with seven 180 ml. portions
5 of water. The benzene extract is dried over magnesium
6 sulfate and concentrated to yield 6-bromopiperonyl methyl
7 ketone.

8 To 106 g. (0.4 mole) of ketone are added 228 ml.
9 water, 75 ml. of 85% hydrazine hydrate and 29.5 g. of
10 potassium cyanide. The mixture is stirred vigorously at
11 room temperature for 18 hours. This mixture is separated
12 by filtration and washed successively with three 60 ml.
13 portions of water and three 50 ml. portions of ether.
14 After drying at 25°C. in air and in vacuo DL- α -(6-bromo-3,4-
15 methylenedioxybenzyl)- α -hydrazinopropionitrile is obtained.

16 L-menthyloxyacetyl chloride (23.18 g., 0.1 mole)
17 is added to a mixture of DL-hydrazinonitrile (29.82 g.,
18 0.1 mole) in 100 ml. of pyridine. Pyridine hydrochloride
19 is removed by filtration and the filtrate is concentrated
20 in vacuo. The residue is crystallized from ethyl acetate
21 to yield L- α -(6-bromo-3,4-methylenedioxybenzyl)-L- α -N²-
22 menthyloxyacetylhydrazinopropionitrile. The acid from the
23 previous step (14.83 g., 0.03 mole) is stirred with
24 fortified (45%) hydrochloric acid (100 ml.) at 0-10°C. The
25 mixture is allowed to warm to room temperature over 2 hours
26 then heated at reflux for 2 hours. The mixture is con-
27 centrated in vacuo to about 15 ml., filtered and the
28 precipitate washed with ice-water and dried. The aminoacid
29 hydrochloride is slurried with water (50 ml.) and diethyl-
30 amine added to reach pH 6.0. After stirring for 1 hour at

1 room temperature the mixture is filtered, washed and dried
2 to yield the L- α -hydrazinopropionic acid. This acid is
3 refluxed with constant boiling hydrobromic acid and worked
4 up to yield L- α -(6-bromo-3,4-dihydroxybenzyl)- α -hydrazino-
5 propionic acid. To the bromohydrazino-acid (3.05 g., 0.01
6 mole) described above in 100 ml. of dioxane is added 1 g.
7 of palladium-on-carbon and triethylamine (1.51 g., 0.015
8 mole). The mixture is hydrogenated at 1 atm. and room
9 temperature until the uptake of hydrogen is 0.01 mole.
10 The mixture is filtered, the catalyst and triethylamine-
11 hydrobromide washed and the filtrate concentrated to dry-
12 ness. The residue is recrystallized from water to yield
13 L- α -(3,4-dihydroxybenzyl)- α -hydrazinopropionic acid, m.p.
14 208° dec.

15 When β -nitrostyrene is used in place of β -methyl-
16 β -nitrostyrene in the above procedure, the product prepared
17 is L- β -(3,4-dihydroxyphenyl)- α -hydrazinopropionic acid.

18

Example 10

19 L-3,4-dihydroxyphenylalanine sesquihydrate (112
20 g., 0.5 mole), phenylnitrosomethane dimer (60.57 g., 0.25
21 mole) and 500 ml. of toluene are placed in a flask and
22 refluxed. By means of a Dean-Stark separator, water is
23 azeotroped away and toluene is returned to the flask. When
24 the theoretical amount of water (1.25 moles) is distilled
25 L- α -(benzylazo)- α -(3,4-dihydroxybenzyl)propionic acid is
26 obtained on concentration of the mixture to dryness in vacuo
27 at a temperature < 50°C. To the azo compound in 5 l. of
28 ether is added 122.94 g. of tetrachloro-0-benzoquinone in
29 1.5 l. of ether. The mixture is stirred at 25°C. for 24

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1 hours. After filtration, drying and recrystallization from
2 methanol, L- β -3,4-benzoquinolyl- α -benzylazopropionic acid
3 is obtained.

4 The acid (31.23 g.; 0.1 mole) in 300 ml. methanol
5 containing 3 g. polyvinyl alcohol-20, 1 g. platinum oxide
6 and 3 g. vanadium (II) chloride is hydrogenated at 1 atm.
7 pressure and 80°C. until the uptake of hydrogen is 0.3 mole.
8 The mixture is cooled to room temperature, filtered, the
9 precipitate washed and the filtrate taken to dryness in
10 vacuo. The residue is recrystallized once from water and
11 a second time from water containing 0.5% sodium bisulfite
12 to yield L- α -(3,4-dihydroxyphenyl)- α -hydrazinopropionic
13 acid.

14 When L- α -methyl-3,4-dihydroxyphenylalanine is
15 used in place of L-3,4-dihydroxyphenylalanine in the above
16 example, the product obtained is L- α -(3,4-dihydroxybenzyl)-
17 α -hydrazinopropionic acid.

18 Example 11

19 A mixture of 3,4-dibenzoyloxybenzaldehyde (159.2
20 g., 0.5 mole), rhodanine (69.0 g., 0.518 mole) and anhydrous
21 sodium acetate (103.6 g., 1.265 moles) in 276 ml. of acetic
22 acid is heated at reflux with stirring for 30 minutes. The
23 mixture is poured into 1.4 l. of boiling water, stirred at
24 95 to 100°C. for 10 minutes and then cooled to 20°C. The
25 product is separated by filtration, washed with water and
26 dried in vacuo at 50°C. to yield 5-(3',4'-dibenzoyloxybenzyl-
27 idene)rhodanine.

28 In 1 l. of water is dissolved the benzylidene-
29 rhodanine (173.3 g., 0.4 mole) purged with nitrogen and

1 containing 120 g. (3 moles) of sodium hydroxide. The mix-
2 ture is heated at 90-95°C. for 15 minutes, rapidly cooled to
3 -15°C. and with strong cooling acidified all at once with
4 300 ml. of concentrated hydrochloric acid. The mixture is
5 cooled to 5°C., filtered, the precipitate washed with four
6 100 ml. portions of ice-water and dried in vacuo at 50°C.
7 to yield cis-trans 3,4-dibenzylxy-a-mercaptocinnamic acid.

8 The mercaptocinnamic acid (117.75 g., 0.3 mole)
9 of the previous step is dissolved in 250 ml. of ethanol,
10 under nitrogen with stirring. Hydrazine (95%, 20.25 ml.,
11 0.6 mole) is added dropwise over 5 minutes. The mixture
12 is heated to 60°, maintained with stirring for 15 minutes
13 and cooled to 20°. The product is separated by filtration,
14 washed with four 75 ml. portions of cold ethanol and two
15 75 ml. portions of ether and dried in vacuo at 50° to yield
16 hydrazinium cis-trans 3,4-dibenzylxy-a-hydrazinocinnamate.
17 The a-hydrazinocinnamate is in tautomeric equilibrium with
18 the a-hydrazone dihydrocinnamate.

19 Methylene iodide (107.2 g., 0.4 mole) and iodine
20 (0.30 g., 0.0012 mole) are added to a mixture of zinc-
21 copper couple (32.6 g. zinc, 0.5 mole) and 330 ml. of
22 anhydrous ether. The ether is refluxed for 30 minutes
23 after the addition is complete. A mixture of hydrazinium
24 salt (84.5 g., 0.2 mole) in 200 ml. of dimethoxyethane is
25 added and the mixture refluxed for 30 hours. The mixture
26 is concentrated in vacuo to remove ether and dimethoxy-
27 ethane. The residue is extracted with 500 ml. of hot
28 methanol. The precipitate is washed with two 100 ml. por-
29 tions of hot methanol. The methanolic filtrate is con-
30 centrated to about half-volume saturated with gaseous

1 hydrogen chloride and allowed to stand at room temperature
2 for 40 hours. The mixture is concentrated to dryness in
3 vacuo and the residue taken up in chloroform-water with
4 the pH of the water layer adjusted to 6 by addition of
5 sodium bicarbonate. The chloroform layer is washed
6 successively with water and saturated salt solution, dried
7 over sodium sulfate and concentrated to dryness in vacuo.
8 The residue is recrystallized from methanol-water to yield
9 methyl DL- β -dibenzylxyphenyl- α -hydrazinocyclopropane-
10 carboxylate.

11 The ester from the previous step (60.67 g., 0.15
12 mole) and methyl L-menthyloxyacetate (18.25 g., 0.08 mole)
13 in 200 ml. of methanol is refluxed for 4 hours. The mix-
14 ture is concentrated to dryness in vacuo, taken up in
15 ether-water, extracted with dilute (1 N) hydrochloric acid,
16 water, 5% sodium bicarbonate and saturated salt solution.
17 The ethereal solution is concentrated to dryness and the
18 residue is crystallized from ethyl acetate-n-hexane to
19 yield methyl L- β -dibenzylxyphenyl- α -N²-L-menthyloxyacetyl-
20 hydrazinocyclopropanecarboxylate.

21 The ester from the previous step (18.0 g., 0.03
22 mole) is refluxed with 54 ml. of 2 N hydrochloric acid for
23 3 hours. The mixture is concentrated to dryness in vacuo.
24 The residue is taken up in chloroform-water, washed with
25 5% sodium bicarbonate, water and saturated salt solution
26 and the chloroform layer dried over sodium sulfate. After
27 concentration in vacuo to dryness the residue is crystal-
28 lized from methanol-water to yield L- β -(3,4-dibenzylxy-
29 phenyl)- α -hydrazinocyclopropanecarboxylic acid.

30 The dibenzylxy compound of the previous step

1. (9.13 g., 0.03 mole) is dissolved in 100 ml. of methanol
2 and hydrogenated over 1 g. of Raney nickel at 25°C. and at 1'
3 to 3 atms. pressure until the uptake of hydrogen is 0.09
4 mole. The mixture is filtered, the precipitate washed and
5 the filtrate concentrated to dryness. L- α -(3,4-Dihydroxy-
6 benzyl)- α -hydrazinopropionic acid is recrystallized from
7 water containing 0.5% sodium bisulfite to yield a product,
8 m.p. 208°C. dec.

9 Example 12A

10 DL- α -hydroxymethyl-3,4-dimethoxyphenylalanine
11 [U.S. Patent No. 3,395,176] (25.5 g., 0.1 mole) is stirred
12 with 100 ml. pyridine and 50 ml. of acetic anhydride. The
13 mixture is warmed to 90°C. and maintained for 1 hour. The
14 mixture is cooled, poured onto ice and extracted with ether.
15 The ether extract is dried and concentrated to dryness in
16 vacuo.

17 The L- β -acetoxy- α -N-acetylamino- α -(3,4-di-
18 methoxybenzyl)propionic acid is obtained from the DL-race-
19 mate by means of the quinine salt.

20 To a slurry of 80 ml. of water, 160 ml. of ether,
21 29 ml. of concentrated hydrochloric acid and 65 g. (0.2
22 mole) of L- β -acetoxy- α -N-acetylamino- α -(3,4-dimethoxy-
23 benzyl)propionic acid at 0-10°C. is added dropwise with
24 vigorous stirring 14.5 g. (0.21 mole) of sodium nitrate in
25 30 ml. of water. The temperature is maintained at 0-10°C.
26 during addition and during one hour of stirring. The ether
27 layer is then separated, the water layer extracted with two
28 100 ml. portions of ether, the combined ethereal extract
29 is washed with saturated salt solution and the ethereal
30 extract dried over magnesium sulfate. The mixture is con-

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1 centrated in vacuo to yield L- β -acetoxy- α -N-nitroso-N-
2 acetylamino- α -(3,4-dimethoxybenzyl)propionic acid.
3 A mixture of 65.5 g. (1.0 mole) of zinc dust
4 and 100 ml. of water is cooled to 10°C. While stirring,
5 53 g. (0.15 mole) of the above nitroso compound in 100 ml.
6 of glacial acetic acid is added while maintaining the
7 temperature at 10-15°C. After addition is finished, the
8 mixture is allowed to warm to room temperature over one
9 hour and then warmed to 80°C. in the steam-bath. The mixture
10 is filtered to remove unreacted zinc, and the precipitate
11 washed with three 25 ml. portions of warm 2 N hydro-
12 chloric acid. The combined filtrate is cooled to room
13 temperature and with cooling basified to pH 6.5. The mix-
14 ture is filtered and the precipitate dried. The residue
15 is extracted with three 200 ml. portions of chloroform.
16 The dried magnesium sulfate extract is concentrated in
17 vacuo to residue which is L- β -acetoxy- α -N¹-acetylhydrazino-
18 α -(3,4-dimethoxybenzyl)propionic acid.

19 A mixture of L- β -acetoxy- α -N¹-acetylhydrazino- α -
20 (3,4-dimethoxybenzyl)propionic acid (35.4 g., 0.1 mole) in
21 200 ml. of acetic acid is refluxed with 100 g. of 50%
22 hydriodic acid and 25 g. of red phosphorous for 4 hours.
23 Insolubles are removed by filtration and the filtrate con-
24 centrated to dryness in vacuo. The residue is dissolved
25 in 500 g. of methanol and treated with 5 g. of ethylene
26 oxide. The mixture is concentrated and water added as the
27 methanol boils away. As soon as some crystals form, the
28 mixture is allowed to cool spontaneously to room temperature
29 then chilled at 0 to 5°C. for 1 hour. The product is sepa-
30 rated by filtration, washed and dried. Recrystallization

- 1 from water containing a small amount of bisulfite yields
- 2 analytically pure L- α -(3,4-dihydroxybenzyl)- α -hydrazino-
- 3 propionic acid, m.p. 208°C.

4 Example 12B

5 A mixture of L- β -acetoxy- α -N-acetylamino- α -
6 (3,4-dimethoxybenzyl)propionic acid (33.9 g., 0.1 mole)
7 and sodium hydroxide (12 g., 0.3 mole) is refluxed for 2
8 hours in 1 l. of water. The mixture is cooled to room
9 temperature, acidified to pH 3 with concentrated hydro-
10 chloric acid and extracted with chloroform. The dried
11 sodium sulfate-chloroform extract is concentrated to dry-
12 ness in vacuo and the residue recrystallized from methanol-
13 water to yield L- α -N-acetylamino- α -(3,4-dimethoxybenzyl)-
14 β -hydroxypropionic acid. This material is recrystallized
15 from methanol-water. By the procedure of Example 12A,
16 this compound is nitrosated and the nitrosoacetylamino com-
17 pound reduced with powdered zinc.

18 To a stirred mixture of L- α -N¹-acetylhydrazino-
19 α -(3,4-dimethoxybenzyl)- β -hydroxypropionic acid (31.2 g.,
20 0.1 mole) in 100 ml. of pyridine is added dropwise at -10
21 to 0°C. 18.95 g. (0.07 mole) of phosphorous tribromide.
22 After 4 hours of stirring at room temperature, the mixture
23 is allowed to warm to 25°C. and the stirring continued over-
24 night.

25 To the mixture is added, with stirring, 100 ml.
26 of water and stirring is continued for 2 hours. The mix-
27 ture is concentrated in vacuo to yield L- α -N¹-acetyl-
28 hydrazino- α -(3,4-dimethoxybenzyl)- β -bromopropionic acid.
29 The residue is taken up in chloroform-water, washed with
30 dilute acid, water and finally salt solution. After drying

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1 over magnesium sulfate, the mixture is concentrated in
2 vacuo. The product is recrystallized from methanol-water
3 or it may be used directly.

4 The residue (37.5 g., 0.1 mole) is then heated
5 in a sealed tube with 500 ml. of concentrated hydrochloric
6 acid as in Example 7 to obtain L- α -hydrazino- α -(3,4-
7 dihydroxybenzyl)- β -hydroxypropionic acid which is used
8 directly.

9 The residue is taken up in 200 ml. acetic acid
10 and refluxed with 100 g. of 50% hydriodic acid and 25 g. of
11 red phosphorous for 4 hours. The remainder of this prepara-
12 tion is completed as in Example 12A.

13 Example 12C

14 L- α -N¹-acetylhydrazino- α -(3,4-dimethoxybenzyl)-
15 β -bromopropionic acid (37.5 g., 0.1 mole) is dissolved in
16 100 ml. of methanol and gaseous hydrogen chloride is
17 added until saturated. The mixture is stirred at room
18 temperature for 24 hours and then evaporated to dryness in
19 vacuo. The residue is recrystallized from methanol-ethyl
20 acetate.

21 Methyl L- α -N¹-acetylhydrazino- α -(3,4-dimethoxy-
22 benzyl)- β -bromopropionate (38.8 g., 0.1 mole) is mixed
23 with 6.0 g. of sodium methylate in 100 ml. of methanol and
24 the mixture refluxed for 5 hours. The mixture is cooled,
25 100 ml. of water is added followed by addition of hydro-
26 chloric acid to pH 8. After concentration to dryness in
27 vacuo the residue is taken up in chloroform-water, the
28 chloroform extracted, washed, dried over magnesium sulfate
29 and concentrated to dryness in vacuo. The residue is
30 crystallized from methanol-water to yield methyl L- α -N¹-

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1 acetylhydrazino- α -(3,4-dimethoxybenzyl)- β -methoxypropionate.
2 A mixture of the above compound (34.0 g., 0.1
3 mole) in 200 ml. of acetic acid is refluxed with 100 g. of
4 50% hydriodic acid and 25 g. of red phosphorous for 4 hours.
5 The workup is completed as described heretofore to yield
6 L- α -(3,4-dihydroxybenzyl)- α -hydrazinopropionic acid.

7 Example 13

8 To a mixture of copper (II) sulfate (159.6 g.,
9 1.0 mole) and L-alanine (178.2 g., 2.0 moles) dissolved in
10 water (700 ml.) is added with stirring 10 N sodium hydrox-
11 ide (200 ml.) to pH 8. The mixture is allowed to cool
12 spontaneously and stand overnight. It is further cooled
13 to 5°C., filtered, washed and dried to yield copper (II) L-
14 alanate (monohydrate).

15 To an ice-cold slurry of copper (II) L-alanate
16 monohydrate (193 g., 0.75 mole) in water (2 l.) is added
17 successively with stirring hydroxylamine-0-sulfonic acid
18 (169.64 g., 1.5 moles) and 2.5 N sodium hydroxide to pH 8.
19 After 10 minutes of stirring at 0-5°, the mixture is heated
20 with stirring at 90°C. for one hour. The mixture is con-
21 centrated to half-volume in vacuo, cooled to 0-5°C. and
22 allowed to stand overnight. The mixture is filtered and
23 the precipitate washed with a little ice-water. On drying
24 in vacuo at 110°C., copper (II) L- α -hydrazinopropionate is
25 obtained.

26 Copper (II) L- α -hydrazinopropionate (134.87 g.,
27 0.5 mole) is stirred with pyridine (1.5 l.) and to the
28 stirred mixture is added at 45-50°C. acetic anhydride (750
29 ml.). The mixture is maintained at 45 to 50°C. for six
30 hours, concentrated to dryness in vacuo and the residue re-

1 crystallized from 50% acetic acid to yield copper (II) L-
2 α -N²-acetylhydrazinopropionate.

3 To copper (II) L- α -N²-acetylhydrazinopropionate
4 (35.38 g., 0.1 mole) in 2 l. of water at 25°C. are added with
5 stirring sodium carbonate (11.2 g., 0.113 mole) and
6 vanillin (38.1 g., 0.25 mole). The mixture is stirred for
7 18 hours at room temperature and heated to 50°C. with
8 stirring. The mixture is cooled to 20°C., brought to pH 7
9 with 2 N sulfuric acid and extracted with three 2 l. por-
10 tions of ether. The aqueous portion is taken to dryness
11 in vacuo and the residue leached in a Soxhlet extractor
12 with methanol. The methanol extract is concentrated to
13 dryness to yield a mixture of copper (II) L- α -N²-acetyl-
14 hydrazinopropionate and copper (II) predominantly L-
15 erythro and threo- α -hydrazino- α -methyl- β -hydroxy- β -(4-
16 hydroxy-3-methoxyphenyl)propionate. The residue is
17 hydrolyzed and reduced in a mixture of 100 ml. of 57%
18 hydriodic acid and 40 g. of red phosphorous. The prepara-
19 tion is worked up as in Example 12A and the product re-
20 crystallized three times from water containing a small
21 amount (0.5%) of bisulfite to yield L- α -(3,4-dihydroxy-
22 benzyl)- α -hydrazinopropionic acid.

23 Example 14

24 DL-3-(3,4-Dihydroxyphenyl)alanine (197.2 g.,
25 1.0 mole) is slurried in 1 l. of pyridine at 25°C. With
26 stirring and some cooling, acetic anhydride (400 g., 3.91
27 moles) is added. The temperature is allowed to rise to
28 45-50°C. and maintained in this range during the addition.
29 The mixture is then heated on the steam-bath at 90-95°C. for
30 one hour, concentrated to near dryness in vacuo and the
31 residue taken up in chloroform-water. The chloroform solu-

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1 tion is washed successively with 1 N hydrochloric acid,
2 water and saturated salt solution. After drying over
3 magnesium sulfate, the solution is concentrated in vacuo to
4 yield 0,0,N-triacetyl DL-3-(3,4-diacetoxymethyl)-N-acetyl-
5 alanine.

6 The triacetyl compound (220 g., 0.794 moles) from
7 the previous step is slurried with a solution composed of
8 267 g. (3.16 moles) of sodium bicarbonate and 3 l. of
9 water. The mixture is stirred at 25°C. for 24 hours, fil-
10 tered and the filtrate acidified to pH 3.5 with concentrated
11 hydrochloric acid. The mixture is concentrated in vacuo to
12 about 300 ml., the residue allowed to stand at 0-5°C. for 18
13 hours, filtered and the precipitate washed with ice-water.
14 The residue is recrystallized from water containing 0.5%
15 sodium bisulfite and dried to yield N-acetyl-DL-3-(3,4-
16 dihydroxyphenyl)alanine.

17 The acetylamino acid (150 g., 0.661 mole) from
18 the previous step is dissolved in 1 l. of 2 N oxygen-purged
19 sodium hydroxide. With cooling and stirring, benzyl
20 chloride (253.18 g., 2.0 moles) is added while the tempera-
21 ture is maintained at 15 to 20°. The mixture is heated
22 with stirring to 90°C. and to it added sodium hydroxide
23 (80 g., 2 moles) and the resulting mixture, with stirring,
24 is refluxed for 18 hours. On cooling to room temperature,
25 the mixture is filtered, concentrated to about 300 ml.
26 in vacuo and acidified with 6 N hydrochloric acid to pH
27 6.0. The mixture is allowed to stand at 0-5°C. for 1 hour,
28 filtered, the precipitate washed with ice-cold water and
29 dried in vacuo at 50°C. The residue is recrystallized from
30 methanol-water to yield DL-β-(3,4-dibenzylxyphenyl)alanine.

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1 D-a-Chlorophenylacetic acid (170.6 g., 1.0 mole),
2 isopropyl alcohol (480.72 g., 8.0 moles) and 4.0 g. 2,4-
3 dinitrobenzenesulfonic acid are refluxed for 30 hours. The
4 residue is concentrated at atmospheric pressure. The mix-
5 ture is cooled, taken up in ether, washed successively with
6 water, 5% sodium bicarbonate water and saturated salt solu-
7 tion. After drying over magnesium carbonate, the ether is
8 distilled at atmospheric pressure and the residue distilled
9 in vacuo to yield isopropyl D-a-chlorophenylacetate.

10 To DL-β-(3,4-dibenzylloxyphenyl)alanine (188.7 g.,
11 0.5 mole) in 1 l. of pyridine is added with stirring iso-
12 propyl D-a-chlorophenylacetate (106.3 g., 0.5 mole). The
13 mixture is heated at reflux for 6 hours, cooled and con-
14 centrated to dryness in vacuo. The residue is taken up
15 in ether and water, the ether layer extracted successively
16 with water, dilute (1 N) hydrochloric acid, water and sat-
17 urated salt solution. After drying over sodium sulfate,
18 the mixture is filtered, washed and concentrated to dryness
19 in vacuo. The residue is recrystallized from methanol-
20 water to yield DL-β-(3,4-dibenzylloxyphenyl)-N-L-(0-isop-
21 propyl-a-phenylacetate)alanine.

22 The substituted alanine (165.8 g., 0.3 mole) is
23 converted to the N-nitroso analog, and to the sydnone as
24 previously described in Example 4 to yield 4-(3',4'-di-
25 benzylloxybenzyl)-3-L-(0-isopropyl-a-phenylacetate)sydnone.

26 The sydnone (56.5 g., 0.1 mole) from the previous
27 step is dissolved in 5 l. of methanol and hydrogenated
28 over Raney nickel at room temperature and 1 atm. pressure
29 until the uptake is 0.5 mole of hydrogen. The mixture is
30 filtered, concentrated to dryness in vacuo and the residue

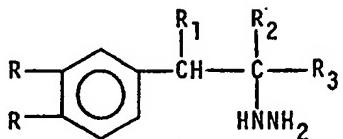
1 recrystallized from water. The product containing DL- and
2 L- β -dihydroxyphenyl- α -hydrazinopropionic acid in preponder-
3 ance is recrystallized from water to constant rotation to
4 yield the pure L-enantiomorph.

5 When the starting material is 3-(3,4-dihydroxy-
6 phenyl)- α -methylalanine in place of 3-(3,4-dihydroxyphenyl)-
7 alanine, the product obtained is L- β -(3,4-dihydroxyphenyl)-
8 α -hydrazinopropionic acid.

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The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A process for preparing the L-stereoisomeric compound of the formula:



where

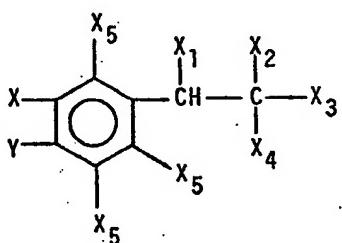
R is hydrogen or

hydroxy;

R₁ and R₂ are hydrogen or
lower alkyl; and

R₃ is carboxy,
loweralkoxycarbonyl,
metaloxy carbonyl or
amido

which comprises reducing the L-stereoisomeric compound of the formula:



where

X and Y are each hydrogen,
hydroxy,
lower alkoxy,
aralkoxy or
keto;

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X and Y together are methylenedioxy, with the proviso that X and Y are not both hydroxy and that when X is keto Y is also keto;

X_1 is hydrogen,

lower alkyl,

hydroxy,

lower alkoxy or

lower alkanoyloxy;

X_2 is hydrogen,

lower alkyl,

hydroxyloweralkyl,

haloloweralkyl,

mercaptoloweralkyl,

loweralkylthioloweralkyl,

loweralkanoyloxyloweralkyl or

tosyloxyloweralkyl;

X_3 is carboxy,

loweralkoxycarbonyl,

aralkoxycarbonyl,

metaloxy carbonyl,

organocatoxycarbonyl,

amido or

cyano;

X_4 is $-\text{NNHNR}_5$,

$-\text{NHNR}_6$,

$-\text{NNH}_2$,

R_5

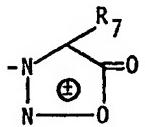
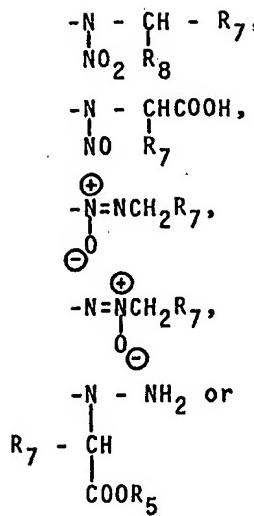
$-\text{NNHR}_5$,

R_5

$-\text{NHNO}$,

$-\text{N}=\text{NCH}_2\text{R}_7$.

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where R₅ is hydrogen, lower acyl or aralkyl,

R_6 is aralkylidene,

R_7 is aryl and

R_8 is halogen; and

x_5 is hydrogen,

halo,

mercapto,

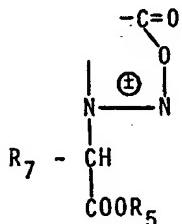
lower alkylthio,

aralkylthio or

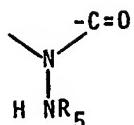
lower alkanoyleth

X_1 and X_2 together are methylene, thus forming a cyclopropyl ring; and

x_3 and x_4 together are



or



where R_5 and R_7 are as described above.

D

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2. A process according to Claim 1

where

 R is hydrogen or

hydroxy;

 R_1 is hydrogen; R_2 is hydrogen or

lower alkyl and

 R_3 is carboxy.

3. A process according to Claim 2

where

 R is hydroxy; R_1 is hydrogen; R_2 is hydrogen and R_3 is carboxythus forming L- β -(3,4-dihydroxyphenyl)- α -hydrazinopropionic acid.

4. A process according to Claim 2

where

 R is hydroxy; R_1 is hydrogen; R_2 is methyl and R_3 is carboxythus forming L- α -(3,4-dihydroxybenzyl)- α -hydrazinopropionic acid.

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